PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003487	22.10.2004	22.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07D239/42, A61K31/505, A61P3/06

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/003487

IAP20 Rec'd PCT/PTO 20 APR 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

rize

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 54

because:

☒ the said international application, or the said claims Nos. 54 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11-14,18-20,23,25-43,47-53
	No:	Claims	1-10,15-17,21,22,24,44-46,54
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-54
Industrial applicability (IA)	Yes:	Claims	1-53
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/IB2004/003487

III. Non-establishment of opinion

Claim 54 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

V. Reasoned statement

Reference is made to the following documents:
D1: WO01/60804
D2: WO03/016317
D3: Hancock and Zografi, J. Pharm. Sci. 86(1) pp. 1-12 1997
D4: US-A-5 260 440

Novelty

It is established case law at the EPO that a document disclosing a low molecular weight organic compound and its preparation method makes this compound available to the public in every desired degree of purity. Thus all documents disclosing rosuvastatin calcium in amorphous form are considered novelty destroying for present claims 1, 2, 5 and 6. For example, D1 discloses this compound as the product of example 10. Furthermore, D1 discloses the necessity of isolating the non-crystalline calcium salt with a purity level and uniformity suitable for formulation, thus anticipating claims 3 and 4. D1 also describes the use of the amorphous calcium salt as HMG CoA reductase inhibitors for the treatment of i.a. hyperlipidemia (p. 2), anticipating claim 54.

D1, example 10 describes the preparation of rosuvastatin calcium by addition of a calcium chloride solution to an aqueous solution of the sodium salt. Although claim 7 refers to a process whereby a solution of rosuvastatin is obtained, claim 15, which is dependent on claim 7, gives filtration as one of the methods of removing the solvent to obtain the amorphous salt. Thus it would appear that claim 7 encompasses processes wherein the rosuvastatin calcium is not dissolved in the solvent. This being the case, D1, example 10 is novelty-destroying for claims 7, 8, 15, 21, 22 and 24. As in this example additional water is added before the filtration, claims 16 and 17 are also anticipated.

In example 10 the sodium salt is obtained by reacting sodium hydroxide with rosuvastatin methyl ammonium salt. Subsequently calcium chloride is added. This example anticipates claims 44-46.

Thus D1 is novelty-destroying for claims 1-8, 15-17, 21, 22, 24, 44-46 and 54.

D2, examples 7 and 8, discloses the obtention of rosuvastatin calcium in an ethanol/water mixture, from which the rosuvastatin calcium is recovered. This anticipates claims 7-10 and 15-17.

Claims 1-10, 15-17, 21, 22, 24, 44-46 and 54 do not fulfil the requirements of Article 33(2) PCT.

Inventive step

In view of their lack of novelty, claims 1-10, 15-17, 21, 22, 24, 44-46 and 54 cannot be inventive.

The technical problem underlying the remaining claims appears to be the provision of further processes for preparing rosuvastatin calcium in amorphous form. General methods for preparing amorphous materials are well known to include milling and rapid precipitation from solution (see D3, p. 1, 1st paragraph). Claims 11-14, 18-20, 23, 31-33 concern processes wherein the rosuvastatin calcium is precipitated out of solution, either by use of a solvent-antisolvent system, by distillation of the solvent or by freeze or spray drying. These claims are obvious in view of the general knowledge of the skilled man, as illustrated by D3. Claims 25-30 concern milling processes which are also obvious over D3. Claims 34-43 and 47 involve the lactonization of the methyl ammonium salt, followed by reaction with a base and calcium salt to give rosuvastatin calcium. The closest prior art appears to be D1, which describes the direct conversion of the methyl ammonium salt to rosuvastatin calcium. The fact that the lactone can be prepared from the corresponding open chain compound is already known from e.g. D4 (col. 4, l. 11-13). There is no information in the application showing that the addition of the extra step of preparation of the lactone has any surprising effect on the outcome of the process. Thus it appears that the extra step serves to establish novelty over the prior art but does not make these claims inventive. Claims 48-53 concern the process of preparing rosuvastatin calcium by treatment

of rosuvastatin with a base and calcium salt, wherein the rosuvastatin is obtained by acidification of rosuvastatin calcium. As already noted above, preparation of amorphous rosuvastatin calcium from a solution containing this compound by precipitation using diverse means such as freeze drying, spray drying, addition of an antisolvent, etc, are obvious over the knowledge of the skilled man illustrated by D3. How the solution is prepared before this precipitation is of no importance to the outcome of the precipitation process. Thus, whilst the method of preparing the rosuvastatin calcium solution is decisive in establishing novelty of the process, it does not make this process inventive.

Claims 1-54 do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-53 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claim 54 is industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.